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Thalamocortical Synchronization and Cognition: Implications for Schizophrenia?

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Cognitive deficits are a core dysfunction in schizophrenia. In this issue of *Neuron*, Parnaudeau et al. (2013) investigated synchronization in thalamocortical pathways in an animal model to address the disconnection between brain regions as a mechanism for working memory impairments in the disorder.

Schizophrenia is a severe psychiatric disorder with a lifetime risk of about 1% that frequently leads to enduring disability for the majority of patients. In addition to the core clinical symptoms of psychosis (delusions, hallucinations, and thought disorder), schizophrenia is associated with a wide range of impairments in cognition, which include working memory (WM), executive control, attention, and dysfunctional sensory processing. Importantly, these dysfunctions are largely immune to current antipsychotic treatments and, as a result, constitute a major determinant for psychosocial functioning and outcome (Green, 1996). The identification of the causes of dysfunctional cognition is, therefore, a prerequisite for the developmental of novel and more effective interventions.

The search for the underlying pathophysiological processes has thus far focused on anatomical and functional abnormalities in circumscribed brain regions. This approach has yielded a large body of evidence implicating various brain areas in cognitive deficits, but the precise circuits and mechanisms underlying these dysfunctions have remained elusive. An alternative approach has been the focus on the role of impaired communication between regions in the pathophysiology of schizophrenia, which most likely involves a disconnection of functional networks (Friston, 1998).

This hypothesis has received support through findings from noninvasive studies using electro- and magneto-encephalography (EEG/MEG) that demonstrate impaired amplitude and synchrony of neural oscillations at low- and high-frequency ranges in patients with schizophrenia (Uhlhaas and Singer, 2010). This is of particular relevance because a large body of evidence suggests that the functional networks underlying perception, attention, and executive processes rely on dynamic coordination through the phase locking of synchronized oscillations (Varela et al., 2001). Accordingly, impairments in this mechanism could lead to a transient failure in the establishment of functional interactions between brain regions, thereby affecting the associated cognitive processes.

In this issue of *Neuron*, Parnaudeau et al. (2013) investigated the hypothesis that thalamocortical synchronization, in this case, between frontal brain regions and the mediodorsal (MD) thalamus, might play an important role in WM and that disturbed synchrony in this circuit might be responsible for WM impairments in schizophrenia. Thalamic functions have recently received renewed interest in systems neuroscience because of their crucial role in gating communication between cortical areas through the synchronization of neuronal responses (Saalmann et al., 2012). Because anatomical and functional abnormalities have been repeatedly demonstrated in the thalamus of patients with schizophrenia (Ronenwett and Csernansky, 2010), abnormal synchronization in thalamocortical pathways could represent an intriguing pathophysiological mechanism for cognitive impairments.

To test this hypothesis, the authors employed a novel pharmacogenetic approach (designer receptors exclusively activated by designer drugs [DREADD]) (Armbruster et al., 2007) that allowed the subtle manipulation of neuronal activity in the MD thalamus, a nuclear complex that projects to the prefrontal cortex and is involved in working memory (Watanabe and Funahashi, 2012). Through the transfection of MD neurons with a mutated muscarinic G protein-coupled receptor, 48% of these neurons could be selectively inhibited by the inert pharmacological compound clozapine-*N*-oxide (CNO). To examine the effects of reduced responsiveness of MD neurons on thalamocortical synchrony, the authors recorded local field potentials (LFPs) and single units from MD and LFPs from the medial prefrontal cortex (mPFC) and dorsal hippocampus. These signals were examined for phase relationships in oscillation frequencies in the theta (4–12 Hz), beta (13–30 Hz), and gamma (40–60 Hz) ranges.

In control animals treated with saline, there was an increase of phase locking of MD units with beta-band oscillations in the mPFC during the choice phase of a T-maze task, which requires the online maintenance of information. The specific relationship between WM and enhanced thalamocortical synchronization was demonstrated in a second experiment during which mice passively explored the T-maze. Here, no increase in beta synchronization between MD and mPFC was observed. Additional analyses of phase lags suggested that MD activity modulated mPFC activity.

In CNO-treated mice, a decrease of MD-mPFC beta-band synchronization occurred with impaired WM performance at longer delays, whereas power spectra in both MD and mPFC were not changed. Moreover, decreased MD activity also resulted in delayed task acquisition. As task performance improved, functional connectivity between MD and mPFC progressively increased. These findings suggest that thalamocortical synchronization at beta frequencies is functionally related to WM and that a reduction in MD activity reduces connectivity between these two brain regions, leading to impaired task acquisition and maintenance of WM-related information.

The study by Parnaudeau et al. (2013) addresses a number of important issues that will be useful for guiding future research on thalamocortical synchronization and its relationship to cognitive functions and dysfunctions. The current data add to the growing body of evidence for an involvement of the thalamus in the synchronization of cortical structures and the importance of temporal coordination for cognitive processes (Saalmann and Kastner, 2011). The frequencies at which these interactions occur are of particular interest. Although previously long-range synchronization during WM between cortical and subcortical structures has been observed at theta-band frequencies (Sigurdsson et al., 2010), increased theta-band synchronization in the current study was only observed during task acquisition and not during the delay phase.

Although the precise computational role of beta-band oscillations during WM needs to be elucidated, it is important to note that beta-band-mediated long-range synchronization has been implicated in the maintenance of visuo-spatial WM items (Salazar et al., 2012). Furthermore, long-range synchronization at beta frequencies is prominently impaired in schizophrenia patients (Uhlhaas et al., 2006), highlighting the potential importance of beta-band synchronization during both normal and abnormal cognition.

An important aspect of the study by Parnaudeau et al. (2013) is the application of the DREADD approach toward fundamental questions in systems neuroscience. Previous studies that tested the relationship between thalamic and cortical functions relied on lesioning entire thalamic nuclei. The selective downregulation of MD units through a targeted pharmacogenetic manipulation represents a significant advance in the determination of causal relations between the activity of defined neuron groups and behavioral functions. Thus, DREADD provides a complimentary technique to optogenetic approaches that have been successfully applied to test the role of neural synchronization in both normal and abnormal physiological states (Yizhar et al., 2011).

The involvement of thalamocortical synchronization in cognitive functions raises a number of interesting issues that are relevant for schizophrenia research. In addition to pronounced impairments in higher cognitive functions, schizophrenia is also associated with marked abnormalities in basic sensory processing (Javitt, 2009). Because of the crucial role of the thalamus in gating sensory responses and attention (Saalmann and Kastner, 2011), it appears promising to also investigate the impact of abnormal thalamic activity on basic perceptual processes and the associated modulation of neural synchrony. Such investigations ideally should be combined with noninvasive measurements in patient populations, because this would allow for the testing of specific pathophysiological hypotheses and the validation of findings from animal models. However, EEG/MEG measurements of thalamocortical interactions remain challenging.

In conclusion, the authors have provided convincing support for a concept that attributes the impairment of cognitive functions in schizophrenia to the disconnection of functional networks through impaired neural synchronization. The established links with related findings from patient samples should encourage efforts to further explore the underlying causes of abnormal synchronization. These are likely to be heterogeneous, but, once identified, it is likely that more effective therapeutic interventions can be designed.

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Hippocampus: Remembering the Choices

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The hippocampus is said to be involved in "navigation" and "memory" as if these were distinct functions. In this issue of *Neuron*, Singer et al. (2013) provide evidence that the hippocampus retrieves spatial sequences in support of memory, strengthening a convergence between the two perspectives on hippocampal function.

In 1989, Richard Morris criticized the notion that place cells—hippocampal principal neurons that fire when a rat occupies a particular location in the environment—had anything to do with memory (Morris, 1989). He emphasized that the existing data showed place cells that tell us only where the animal is at the present time and offer no information about where it might go based on memories of what is found at distant locations. This and many other disconnects have long characterized a separation between "navigation" and "memory" literatures of hippocampal function. However, in the current issue of *Neuron*, observations by Singer et al. (2013) seem to address Morris's concern, providing compelling evidence that hippocampal neural ensembles retrieve memories of alternative paths, composed as different sequences of place cell activations, which could lead the animal to a desired goal.

Singer et al. (2013) recorded from CA1 and CA3 principal cells in rats performing a spatial alternation task in a "W-shaped" maze (Figure 1). They examined neuronal activity during local field potential events known as sharp-wave ripples (SWRs), in which several earlier reports have shown a speeded "replay" of neuronal firing sequences that had occurred in earlier experiences. Specifically, their analyses focused on SWRs when the rat was relatively still while outbound on the center arm, heading toward the critical choice between the left or right arm as having the next reward. During these SWR events, they identified replays as coactivations of place cell activity that typically occurred during actual runs toward the left or right goals. There were three main findings. First, more replays occurred preceding subsequent correct choices than incorrect choices and, in the latter, the likelihood of replay was at chance level. Second, there were usually multiple replays at these times, corresponding to both the correct and incorrect choice paths. Third, replays were common early in learning but no longer appeared when rats had mastered the task. Thus, associated with the course of learning, the hippocampus replays alternative paths just before a critical choice between those paths is made, and the occurrence of replay increases the accuracy of the subsequent choice.

These findings build on many earlier observations about hippocampal replay, including, in particular, that hippocampal neural ensembles replay both recent paths and paths not recently taken (Gupta et al., 2010). Also, the occurrence of replays is greater after novel experiences and correlates with memory performance (Dupret et al., 2010). And replays of alternative paths have also been observed when rats investigate possible choices during vicarious trial and error at a critical decision point (Johnson and Redish, 2007). Here the trial-by-trial prediction of accuracy by the proportion of replays of alternative paths suggests that hippocampal replay reflects the retrieval of multiple relevant memories that can be evaluated to guide the correct subsequent choice, and this is of particular value early in learning (Figure 1).

The findings on hippocampal replay and its association with memory are paralleled by several observations on trajectory-dependent activity of place cells (reviewed in Shapiro et al., 2006). In these studies, rats traverse overlapping routes through a maze and a typical observation is distinct place cell firing sequences for